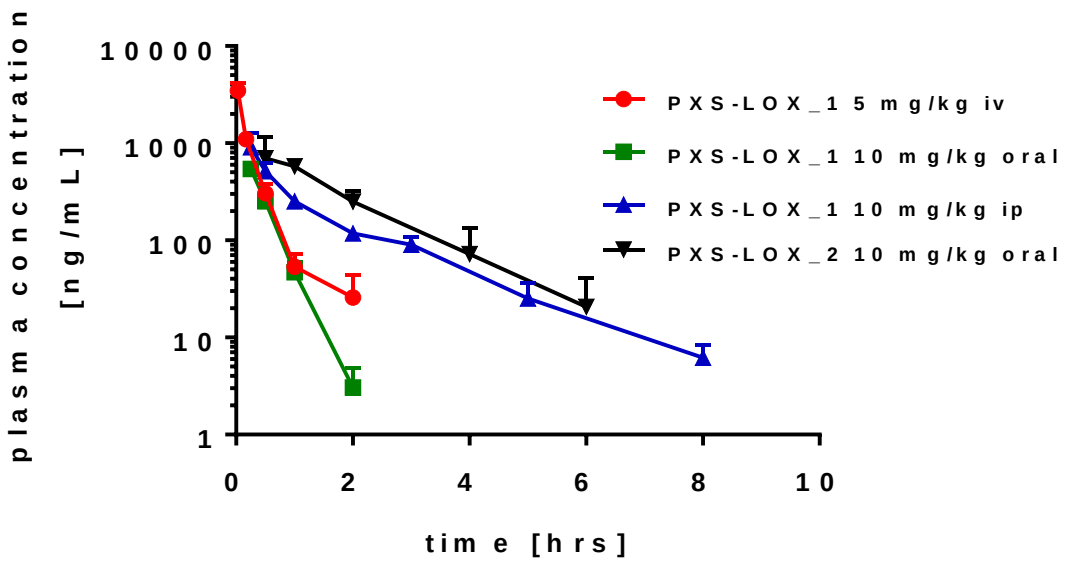
Supplemental (SP) Table 1

pIC50 ± SD (µM)	PXS-LOX_1	PXS-LOX_2	BAPN
Bovine LOX	5.8 ± 0.11 (1.5)	5.8 ± 0.03 (1.7)	5.7 ± 0.13 (2.2)
Mouse LOX	5.7 ± 0.06 (2.1)	5.7 ± 0.03 (1.9)	5.5 ± 0.07 (3.3)
rhLOXL1	5.8 ± 0.05 (1.5)	5.8 ± 0.03 (1.6)	5.6 ± 0.13 (2.5)
rhLOXL2	6.5 ± 0.08 (0.34)	6.3 ± 0.09 (0.50)	6.4 ± 0.12 (0.38)
rmLOXL2	6.2 ± 0.09 (0.57)	5.9 ± 0.06 (1.2)	6.1 ± 0.18 (0.80)
rhLOXL3	6.2 ± 0.13 (0.60)	5.7 ± 0.03 (1.8)	6.3 ± 0.14 (0.51)
rhLOXL4	6.8 ± 0.08 (0.14)	6.7 ± 0.11 (0.20)	6.5 ± 0.09 (0.29)
SSAO	<4.5	4.8 ± 0.17 (17)	S
DAO	<4.5	<4.5	S
MAO-A	<4.5	<4.5	<4.5
MAO-B	<4.5	<4.5	<4.5

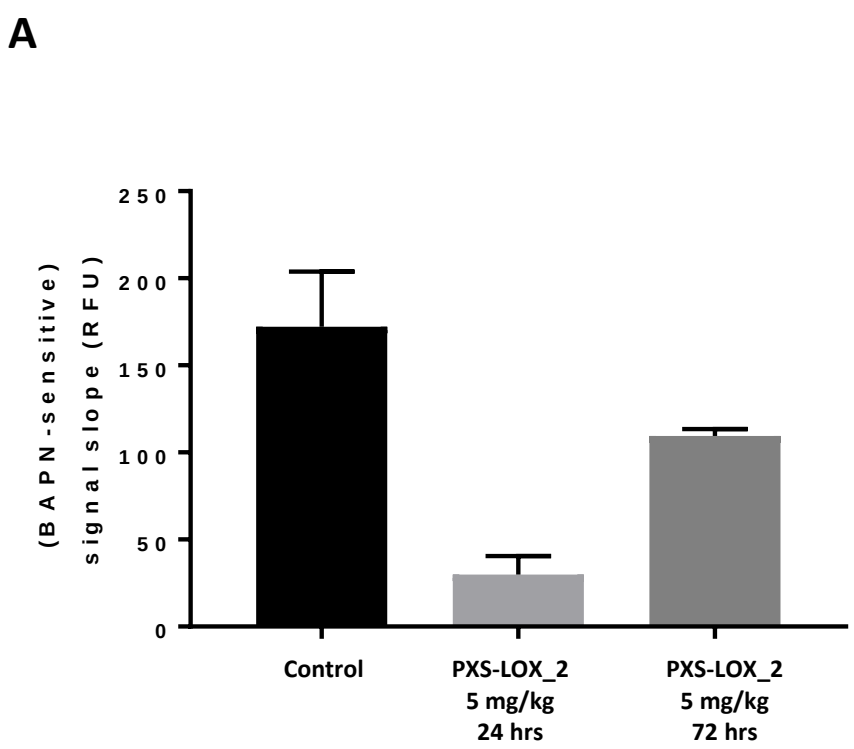
SP Table 1: Inhibition of LOX and other amine oxidases by PXS-LOX_1 and PXS-LOX_2 compared to BAPN. Compounds were tested after 30 min pre-incubation against recombinant (r) or native (isolated from supernatant of fibroblasts) by size exclusion chromatography as previously described(19). Considering that pIC50 = -log(IC50) data show that the selectivity within the lysyl oxidase family varies maximally 10 fold. Methods to determine amine oxidase activity have been described in(19). Substrates were benzylamine (SSAO, MAO-B) putrescine (LOX, LOXL1, LOXL2, LOXL3, LOXL4and DAO) and tyramine (MAO-A). S: compound is a substrate; SSAO: semicarbazide-sensitive amine oxidase (gene name: AOC3); DAO: diamine oxidase (gene name: AOC1); MAO-A: monoamine oxidase A; MAO-B: monoamine oxidase B

Supplemental (SP) Figure 1



SP Figure 1: Pharmacokinetic profile of PXS-LOX_1 and PXS-LOX_2 after different routes of administration. Wistar male rats (160-250 grs) received a single administration of the drug intravenous (iv), intraperitoneal (ip) or by oral gavage (oral). See rational in SP Figure 2 for using rats. Plasma was taken from the tail vein at the indicated time points and the concentration of the inhibitor was measured by LC/MS/MS and plotted on the y-axis. The plot shows that initial concentrations of the inhibitors were high and quickly declined after iv administration ($t_{1/2}$ < 1hr). Data are averages+/-SD. IP administration of PXS-LOX_1 caused the same concentration time course as the oral administration of PXS-LOX_2, suggesting that the oral absorption of PXS-LOX_2 is a good choice.

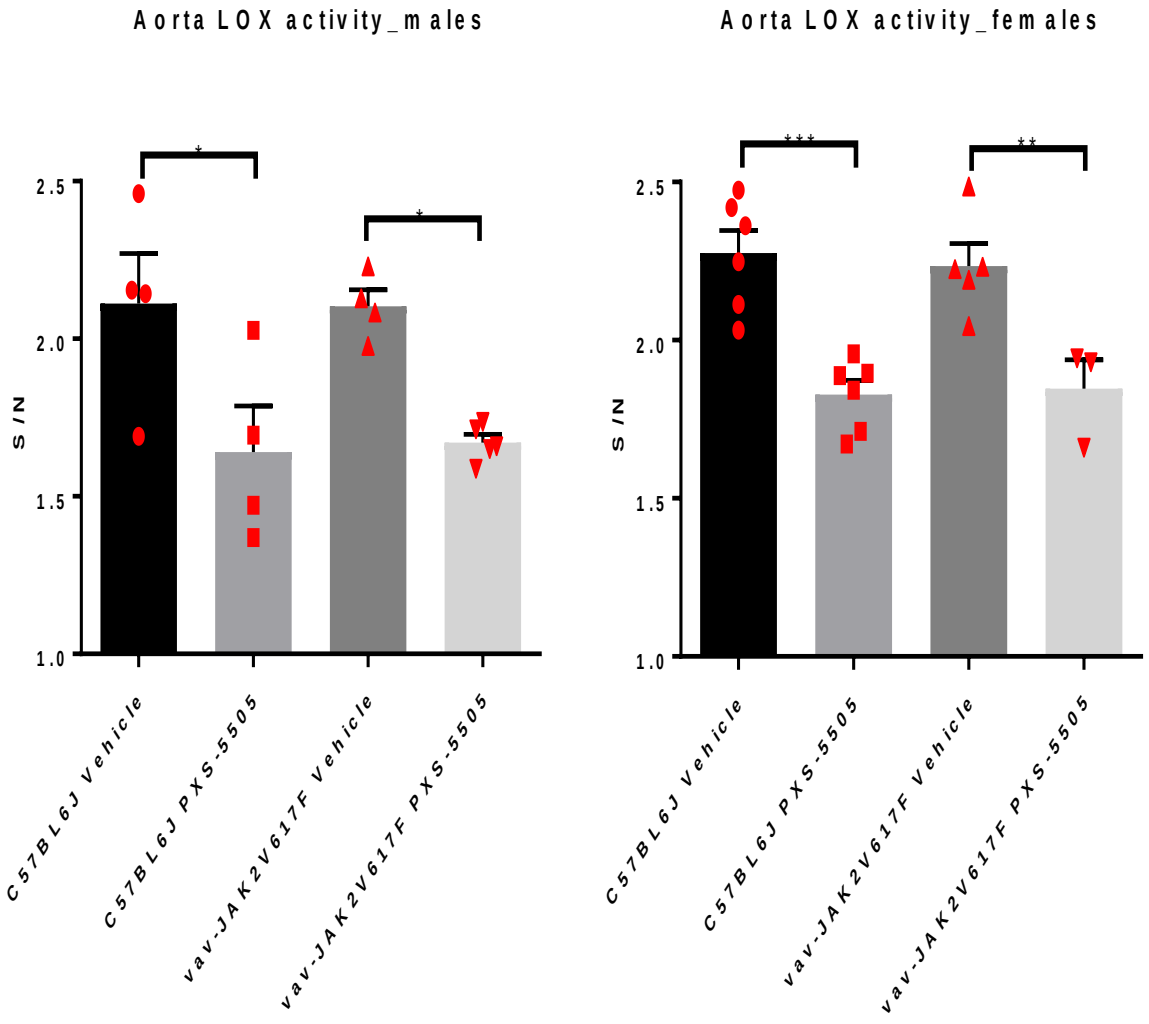
Supplemental (SP) Figure 2



SP Figure 2: A. LOX activity in treated rats. In order to determine an appropriate dose and dosing frequency, PXS-LOX_2 was given by oral gavage to Wistar male rats (160-250 grs) and lysyl oxidase activity was measured in the aorta. The initial focus was on rat aortas as source of signal considering ample of tissue, compared to mouse aorta. On the day of the experiment, aortas were cleaned, snap frozen in liquid nitrogen and pulverised and further homogenised in 0.15M NaCl, 50mM Na Borate, pH=8.0 using metal beads. All activities were performed on ice, and in buffer containing protease inhibitors (PMSF: Sigma P7626, 0.25mM; Aprotinin: Sigma A6279, 1 µL per mL). After three washes and spinning (10,000*g* for 10 minutes @ 4^{o}C), the remaining pellet was resuspended in 50mM Na Borate, 6M urea, pH=8.2 and incubated for 3hrs at 4^{o}C in a rolling tube. The mixture was then centrifuged for 20 minutes at 4^{o}C, 10,000*g*, the supernatant collected and diluted in 2.4M urea and 50mM Na Borate buffer pH 8.0. Lysyl oxidase activity, measured as previously described(19), in non drug-treated animals is constant. The control refers to the animals treated with placebo and sacrificed at 24 hrs. Signal is expressed as slope (RFU: relative fluorescence units) of the tissue sample minus the slope of the background. PXS-LOX_2 caused a strong reduction in the lysyl oxidase activity, which lasted for more than 24 hrs. Therefore, 4 doses a week seem to provide a sufficient lysyl oxidase inhibition. Data are averages+/-SD (n=3).

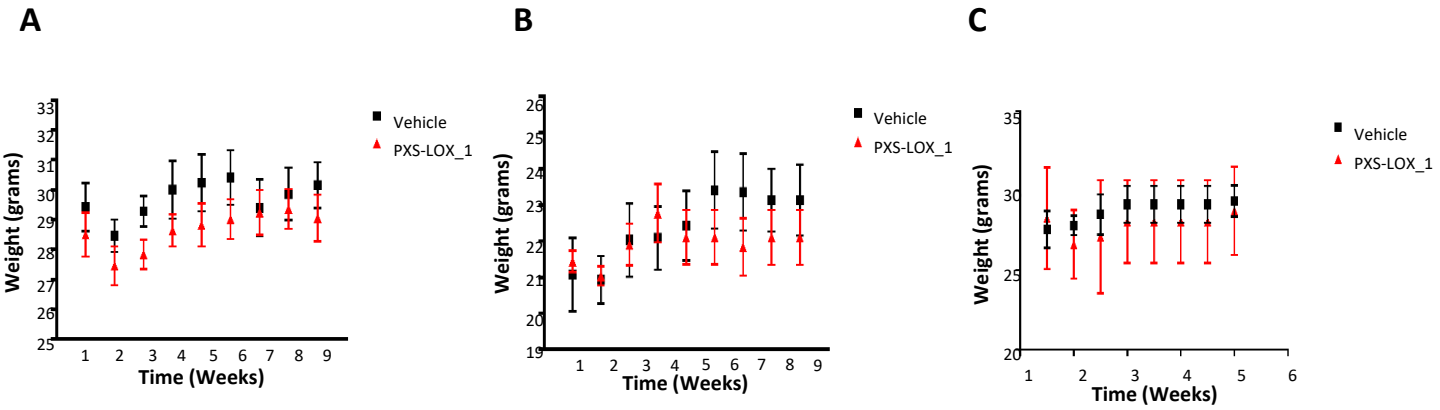
Supplemental (SP) Figure 2

B



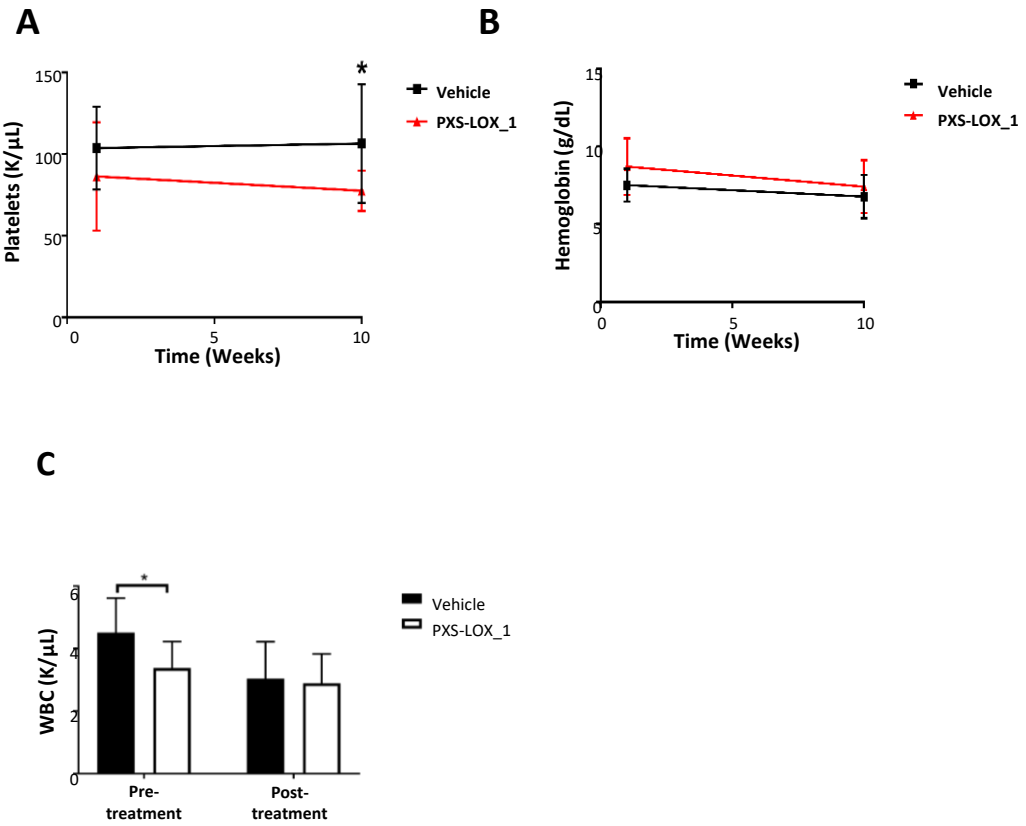
SP Figure 2: B. LOX activity in treated-mice. Each mouse aorta was pulverised in liquid N_2, washed three times with cold wash buffer (50mM $Na_2B_4O_7$ and 150mM NaCl, pH8.0, 1mL each time) containing protease inhibitor (0.25mM PMSF and 1µL/mL aprotinin) and centrifuged at 20,000*g* at 4°C. The supernatants was discarded and the tissue pellet extracted with extraction buffer (50mM $Na_2B_4O_7$ and 6M urea, pH8.2), at three times buffer volume to tissue weight ratio, for 3 hours at 4°C. The mixture was centrifuged at 20,000*g*. Pargyline and mofegiline at final concentrations of 0.5mM and 1µM, respectively, were added to the supernatant. Each supernatant was incubated with or without 600µM β-aminopropionitrile (BAPN) for 30 minutes at 37°C, and assayed with a reaction mixture of amplex red, horseradish peroxidase and putrescine at final concentrations of 60µM, 0.75U/mL and 5mM, respectively, in 50mM $Na_2B_4O_7$ and 1.2M urea final concentration. Fluorescence was measured every 2.5 minutes for 30 minutes at 45°C (with excitation and emission at 544nm and 590nm, respectively), and the signal (kinetic value without BAPN) to noise (kinetic value with BAPN) ratio indicated the LOX activity in the aortic tissue. Data are averages+/-SD for the indicated number of mice (red indicators).

Supplemental (SP) Figure 3



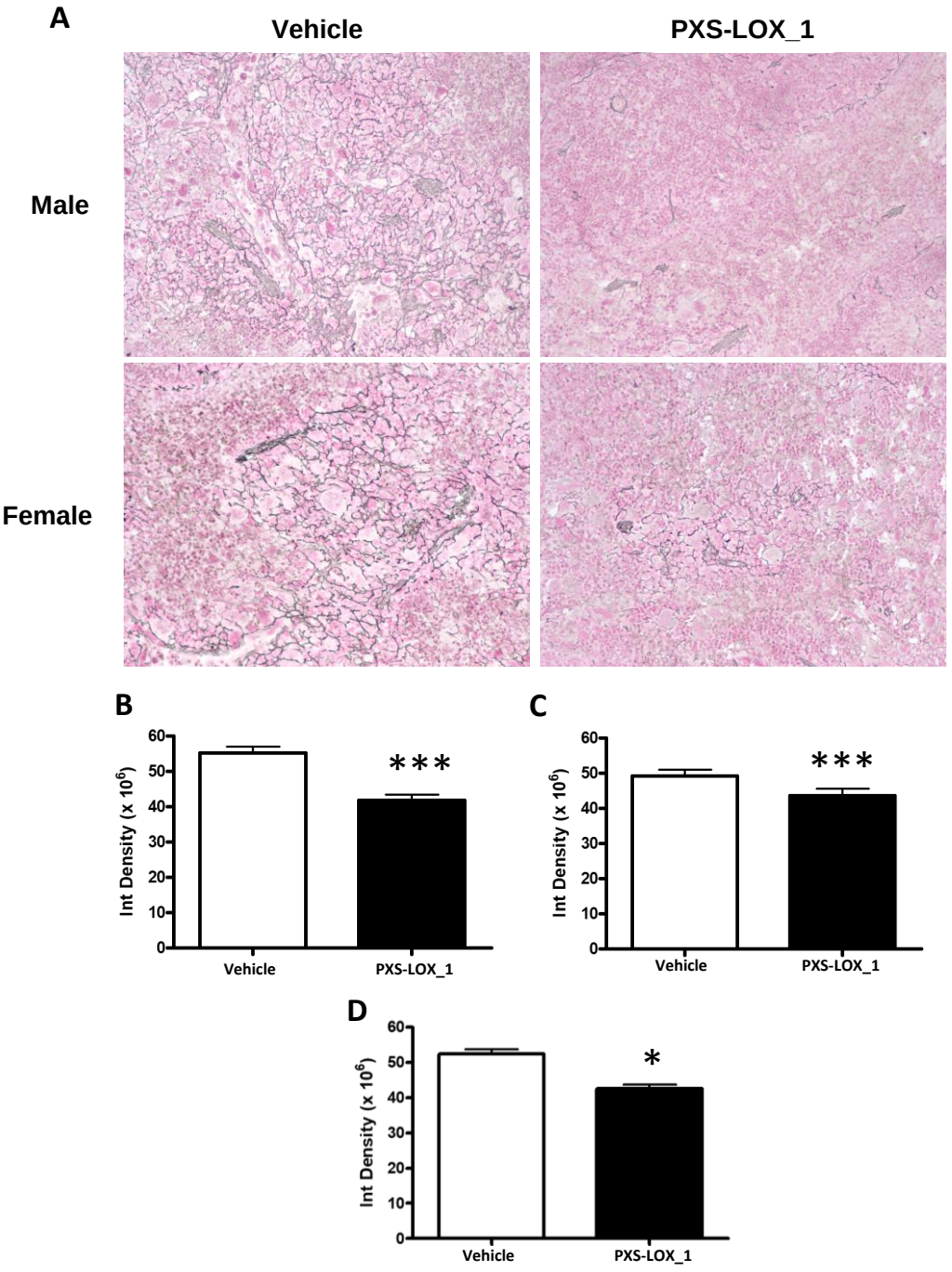
SP Figure 3: Weights of GATA-1low mice during the course of drug treatment. Mice were weighed on a weekly basis and doses of drug were adjusted accordingly. There was no difference in weights between PXS-LOX_1-treated mice and vehicle-treated mice. GATA-1low male weights (**A**), GATA-1low female weights (**B**) and JAK2V617F mice weights (**C**). Data are averages ± SD for GATA-1low (9 vehicle, 8 PXS-LOX_1-treated) and JAK2V617F mice (4 vehicle and 4 PXS-LOX_1-treated).

Supplemental (SP) Figure 4



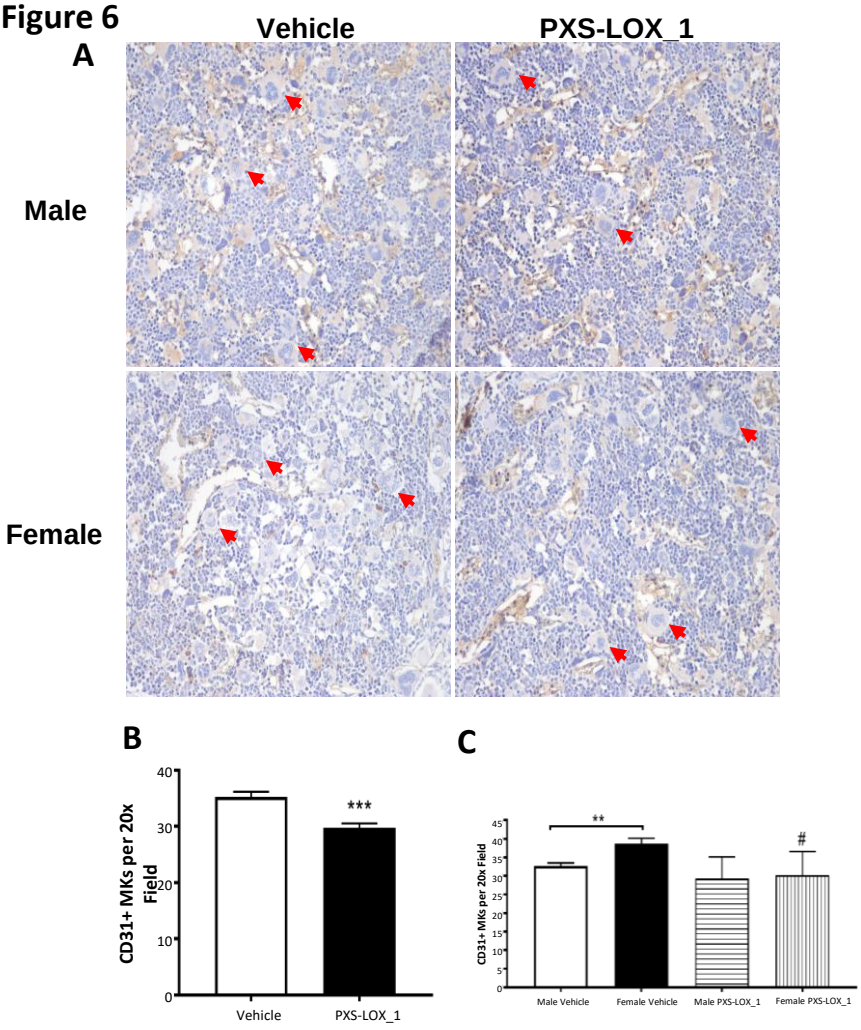
SP Figure 4: Blood cell counts in PXS-LOX_1-treated GATA-1low mice. Blood was collected from mice before the start of treatment and at the time of sacrifice. There was a modest decrease in platelet count at sacrifice in GATA-1low mice treated with PXS-LOX_1 vs vehicle-treated GATA1low mice (**A**) * $p < 0.05$. There were no differences in hemoglobin between PXS-LOX_1- and vehicle-treated GATA-1low mice (**B**). Data are averages ± SD for the number of mice described in SP Figure 3.

Supplemental Figure 5

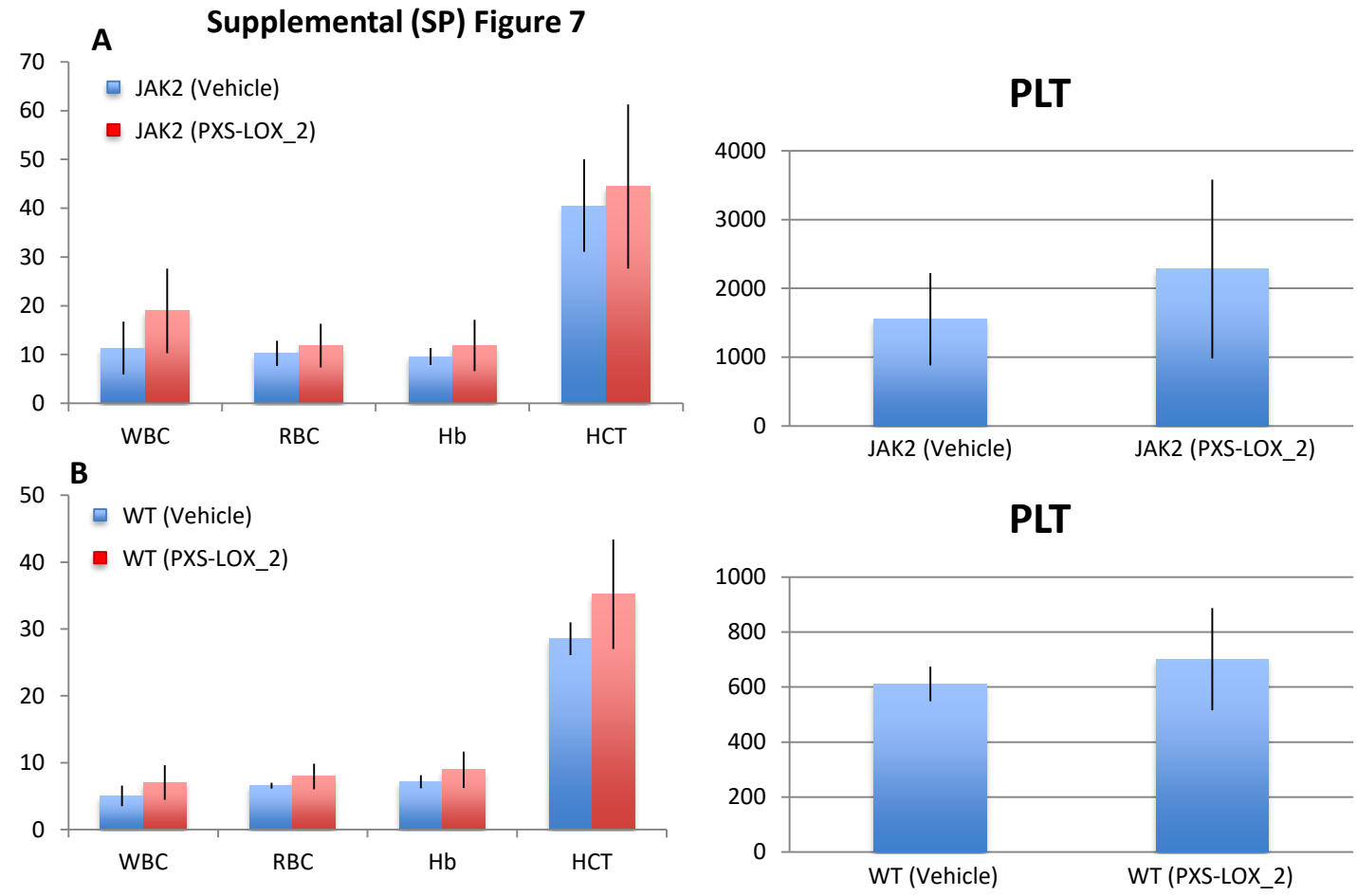


SP Figure 5: Splenic fibrosis is reduced in PXS-LOX_1-treated GATA-1low mice. (**A**) GATA-1 low mouse spleen sections were subjected to reticulin staining (shown is a representative image). (**B**). Male GATA-1low PXS-LOX_1-treated mice had significantly less spleen fibrosis than vehicle-treated mice. (**C**) Similarly, PXS-LOX_1 also reduced splenic fibrosis in female GATA-1low mice. (**D**) After pooling both sexes, these differences were still statistically significant. Data are averages ± SD for n = 20 images per animal, n = 9 vehicle-treated (5 male, 4 female), 8 PXS-LOX_1-treated (5 male, 3 female). * $p < 0.05$, *** $p < 0.001$ using student t-test.

Supplemental (SP) Figure 6



SP Figure 6: Immunostaining and counting of megakaryocytes in PXS-LOX_1-treated GATA-1low mice. Immunostaining was performed using anti-CD31 to view both megakaryocytes and the vasculature in GATA-1low mouse femur sections (**A**), and 20 random 20x images were taken per mouse. CD31-positive morphologically recognizable megakaryocytes (red arrows) were counted. GATA-1low mice treated with PXS-LOX_1 had significantly lower numbers of CD31-positive bone marrow megakaryocytes compared to vehicle-treated GATA1low mice (**B**). Female GATA-1low vehicle-treated mice had more CD31-positive bone marrow megakaryocytes compared to male GATA-1low vehicle-treated mice. Female PXS-LOX_1-treated mice had decreased CD31-positive bone marrow megakaryocytes compared to female vehicle-treated mice. No significant difference between male vehicle- and PXS-LOX_1-treated mice was seen (**C**). Data are averages ± SD, n = 4 GATA-1low vehicle-treated mice, and 4 GATA-1low PXS-LOX_1-treated mice.** $p < 0.01$, *** $p < 0.001$, # $p < 0.001$ vs respective sex vehicle.



	WBC	RBC	Hb	HCT	PLT
t.test comparing drug-treated and vehicle-treated JAK2V617F mice	0.047995336	0.394972769	0.246567097	0.561803358	0.166053433
t.test comparing drug-treated and vehicle-treated WT mice	0.048367047	0.037536314	0.061776836	0.023248268	0.161203672

SP Figure 7: Blood cell counts in PXS-LOX_2-treated JAK2V617F mice. Blood was collected from male (**A**) and female (**B**) mice before the start of treatment and at the time of sacrifice. There was a tendency for an increase in platelet count at sacrifice in PXS-LOX_2-treated JAK2V617F vs. vehicle-treated mice. The following mice were analyzed in each group: 9 vehicle-treated and 7 PXS-LOX_2-treated JAK1V617F and 10 vehicle-treated and 11 PXSLOX_2-treated C57BL6J animals. Males and females were analyzed in the same group. WBC: white blood cells; RBC: red blood cells; Hb: hemoglobin; HCT: hematocrit; PLT: platelets.